FAMILIAL AGGREGATION OF FRACTURES: A PILOT STUDY

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Familial Aggregation of Fractures: A Pilot Study

By

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ABSTRACT

Background: Childhood fractures are common and preventable. They are a significant cause of morbidity and are relatively understudied. Some children may have readily identifiable risk factors and examination of this possibility will help our understanding of pediatric fractures.

Objectives: To investigate familial, environmental and other complex influences on fracture risk in children.

Design/Methods: Case-control study of 150 children with and without fracture.

Results: Children with fractures were more likely to have a parental history of fracture (46.8% of cases versus 31.0% of control; p=0.007). Odds ratios for fracture were 2.2 (p= 0.036), 2.03 (p=0.035) and 3.7 (p= 0.009) if the child's mother, father or both parents fractured respectively. Cases were twice as likely to have siblings and 1.5 times as likely to have first-degree relatives with fracture. Increased parental fracture burden was seen in families of children with multiple fractures. Groups did not differ with respect to environmental influences on fracture risk.

Conclusions: There appears to be an increased familial clustering of childhood fractures as children with fractures are more likely to have parents and siblings with childhood fractures. Explanations for this association between parental fractures and increased risk of fracture for their children are currently unknown. This association should be validated in larger sample sizes and the relative impact of genetic, environmental and behavioral factors need to be further elucidated.

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BMD	Bone Mineral Density
OR	Odds Ratio
RR	Risk Ratio
RCT	Randomized Controlled Trial
CI	Confidence Interval
DNA	Deoxyribonucleic Acid
HPA	Hypothalamic-Pituitary-Adrenal
PTH	Parathyroid Hormone
BMC	Bone Mineral Content
GH	Growth Hormone
ER	Estrogen Receptor
PED	Pediatric Emergency Department
MZ	Monozygotic
DZ	Dizygotic
ADHD	Attention Deficit Hyperactivity Disorder
CYP	Cytochrome P450

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CHAPTER 1: General Introduction

Chapter 1:1 Background: Rationale and relevance to child health

Fractures are common, preventable and are a significant cause of morbidity in all populations. Fractures cause unnecessary pain and suffering. The treatment and follow- up is expensive. The less obvious costs (i.e. indirect costs) to our society in terms of lost productivity must also be considered. Fractures sustained in childhood may have both immediate and long-term effects, however childhood fractures have been relatively understudied. The question remains as to whether fractures are just a normal part of an otherwise healthy childhood, or whether risk factors exist which could help to identify those who may benefit from early focused preventative interventions.

Chapter 1:2 Epidemiology of childhood fractures differs from adults

Fracture rates peak during adolescence and old age although fracture patterns differ considerably between the two populations. Most fractures occur during normal play or sport with minimal or moderate trauma (Rauch et al 2001). Fractures make up 10-25% of all pediatric injuries: 42-51% of boys and 27-40 % of girls experience at least one fracture during childhood (Landin 1983; Tiderius et al 1999; Jones et al 2002; Cooper et al 2004).

In childhood, 75% of fractures affect the upper limbs (Yeh et al 2006). Forearm fractures are the most common (25-35% of all fractures) (Cheng, & Shen 1993; Cooper et al 2004; Khosla et al 2003) and peak at age 10-12 years in girls and 13- 15 years in boys, the periods for peak height velocity for both sexes (Cooper et al 2004; Landin 1983; Rauch et al 2001; Tiderius et al 1999). Other frequent sites of fracture in children are the fingers and hands, clavicle and humerus (Cheng, & Shen 1993; Landin 1983; Landin 1997). Fractures of the hand bones are more common in teenagers whereas humerus fractures are more common at a younger age (Cheng, & Shen 1993). As children grow, adjusting muscle dynamics and resultant changes in

falling and self-protection, may explain age-related fracture variations. Fractures of the axial skeleton and lower limbs are far less common in children and are usually associated with considerable traumatic force, disease processes or medications (Cooper et al 2004; Tiderius et al 1999). Children at increased risk of fracture may be those with delayed bone maturation (Taes et al 2010) and children with long narrow bones fracture more easily than children with shorter broader bones (Skaggs et al 2001; Taes et al 2010).

Adolescents are more susceptible to fractures than younger children (Cheng, & Shen 1993; Landin 1983; Landin 1997). The pubertal growth spurt results in a transient deficit in bone mass relative to growth of bone. Pubertal characteristics include an increased demand of new bone for minerals, increase in growth regulating hormones, increased bone turnover and reshaping of the distal metaphyses (Bass et al 1999; Fournier et al 1997; Magarey et al 1999; Matkovic 1996; Rauch et al 2001). Boys may suffer more fractures because of more high risk taking behaviors and higher peak growth rates than girls.

Ninety-eight percent of incidents causing fractures in children result in only a single bone fracture per event (Cheng, & Shen 1993). Overall, fracture incidence rates are increasing, with a 56% increase for girls and a 32% increase for boys from 1969-1999 in the United States (Cheng, & Shen 1993). Similar increases in other countries may signal the influence of environmental rather than genetic factors (Brudvik, & Hove 2003; Hagino et al 2000; Lyons et al 1999).

Chapter 1:3 Early development influences fracture risk

Programming or persistent changes in phenotype, caused by environmental pressures acting at critical periods of rapid cell division during early development, is thought to contribute

to the development of osteoporosis and fracture risk later in life (Lucas 1991; Lucas 2005). In gravid animal models, small variations in diet can result in permanent changes in the metabolism; physiology and physical build of the offspring (Bateson 2001; Bateson 2007; Lucas 2005). Periods of plasticity, consisting of sensitive interactions between the genome and the variable environment can result in an unpredictable (and irreversible) phenotype for a given genome. Small changes or deficiencies in the environment can affect development prior to implantation by changing DNA epigenes and gene expression, by changing tissue differentiation, by changing sensitivity to hormones during fetal growth or by changing homeostatic mechanisms such as the hormonal hypothalamic-pituitary-adrenal axis (HPA), parathyroid hormone (PTH), vitamin D or growth hormone (GH) axes (Cooper et al 2005). Periods of rapid growth are more vulnerable to a sub-optimal environment (Cooper et al 2005).

Growth during intrauterine and early postnatal life may be the most influential stage for bone mineral accrual across the lifespan. By the second trimester a maternofetal gradient, with higher fetal than maternal calcium concentration, has been established (Cooper et al 2005). This gradient is influenced by low fetal PTH and variations in calcium concentration presented to the fetal circulation secondary to maternal PTH. By 24 weeks, 66% of total body calcium, phosphorous and magnesium have accumulated in a healthy full term infant under the partial genetic influence of regulatory hormones including $1,25(OH)_2$ vitamin D_3, PTH and calcitonin (Cooper et al 2005). In a cohort of 216 children, reduced whole body BMC at 9 years of age was associated with lower umbilical venous serum calcium, lower maternal 25-hydroxy vitamin D, reduced maternal height, lower preconception weight, reduced maternal fat stores in late pregnancy, history of smoking and lower income (Javaid et al 2006).

The third trimester is the time of greatest bone acquisition, and thus bone mass at birth is negatively influenced by premature gestational age (Demarini 2005). Population studies including a large twin study have demonstrated the association between birth weight and bone mass (Antoniades et al 2003; Cooper et al 1995; Cooper et al 1997; Dennison et al 2005).

Physiologic studies have demonstrated that birth and infant weight at one year may be predictors of basal GH and cortisol in late adult life which in turn influence bone loss rate. It is proposed that intra-uterine environmental features alter the sensitivity of the growth plate to GH and cortisol, reducing peak size, mineralization and accelerating bone loss in later life (Dennison et al 2005; Fall et al 1998; Phillips et al 1998). Other negative influences on neonatal bone mass are birth during winter months and maternal lifestyle such as maternal smoking, poor nutrition, caffeine and diabetes (Godfrey et al 2001).

Growth rates in childhood have been linked with risk of hip fracture in later life. From a cohort of 7000 men and women and after adjustments for age and gender, the major determinants of hip fracture risk were independently, tall maternal height, low rate of childhood growth and short length at birth (Cooper et al 2001). It was also observed that even though fracture subjects were shorter at birth they were of average height by age 7 suggesting that the imbalance between growth of the skeletal envelope and the ability to mineralize bone may be an underlying issue. Thus a mechanism of early endocrine programming may influence risk of hip fracture later in life.

Chapter 1:4 Variations in bone mass, strength and structure influence fracture risk

Metabolic bone diseases predispose to fracture largely due to a decrease in the mass and strength of the skeleton and musculature. From birth through young adulthood, up to about 30

years of age, bone formation continues to predominate, resulting in a steady accumulation of bone mass. Most bone mass, in fact, is accumulated by early adulthood (Bianchi 2007; Bachrach 2007a; Bachrach 2007b; Seeman 2002; Kalkwarf et al 2007). After the mid-thirties, bone mass typically begins to decline slowly. This process is accelerated after menopause. Both genetic and lifestyle factors (e.g. diet and physical activity) influence the development of peak bone mass and the rate at which bone is lost (Black et al 2002; Fuchs, & Snow 2002; Fuchs et al 2001; Kalkwarf et al 2003; Heaney, & Weaver 2005; Matkovic 1996; Lucas 1991; Ma, & Jones 2004; Wyshak 2000; Clark et al 2008b).

Bone strength is determined by both bone mineral density and the complex micro architectural properties of bone. The distribution patterns of bone mass, not just its quantity, are important in predicting whole bone strength (Goldstein et al 1993; Kreider, & Goldstein 2009). Some studies have correlated measures of density and architectural organization with trabecular stiffness and strength (Seeman 1997). Differences between males and females have also been documented (Goulding et al 1998; Goulding et al 2000; McCreadie, & Goldstein 2000; Nguyen, & Eisman 2000; Seeman 2002). This micro-architectural strength is determined by the complex interactions of the connectivity and brittleness of the trabecular network, the vitality of the bone cells, the ability to repair micro-cracks, the crystal size and shape and the structure of the bone proteins. The fat cells, vasculature, neuronal pathways and bone marrow cells probably also influence the quality as well as the quantity of bone. The micro- architecture, a distinct entity, appears to differ between osteoporotic and normal individuals and with age (Kreider, & Goldstein 2009).

Bone fragility and susceptibility to fracture occurs at the most vulnerable point in the balance between BMD and micro-architecture strength (Brandi 2009). Susceptibility to fracture

is also influenced by bone size, bone remodeling, muscle mass and coordination, torque and force on bone, and the endocrine system (Burr 1997). This multi-component balance and the ability to readjust the balance, changes throughout the lifespan and differs across gender and ethnicity. Many features contributing to bone integrity, appear to have genetic contributions, but the proportion and distribution of these contributions are not well understood or studied.

BMD, although a useful tool for prediction of fracture, and the most common proxy thereof in the literature, provides only a two dimensional view of a three-dimensional mass of bone and is thus limited in full representation of the micro-architecture of bone. Decreases in BMD were initially thought to have been a problem mainly of the post- menopausal woman due to environmental and estrogen effects, however studies have suggested that BMD is 80% determined genetically with 20% influenced by environmental factors (Nguyen, & Eisman 2000). Unfortunately, little is known about the genetic contribution to the micro-architectural properties of bone. In fact loss in bone mass alone may not be indicative of increased fracture risk if compensatory geometric factors are present (McCreadie, & Goldstein 2000; Seeman 1997; Seeman 2002). Thus if variations in BMD and force are removed as confounding risk factors in the pathogenesis of fractures, the status of an individuals' bone micro-architecture may indeed be significant.

Low BMD significantly increases fracture risk in adults (McCreadie, & Goldstein 2000; Seeman 1997; Seeman 2002) and case-control evidence now suggests that children who fracture repeatedly have reductions in BMD (Clark et al 2008a; Goulding et al 1998; Goulding et al 2001; Ma, & Jones 2004). Goulding at al compared girls with forearm fractures to fracture free controls and found that BMD was significantly lower in cases, supporting the view that low bone density may contribute to fracture risk in childhood (Goulding et al 1998). Goulding then followed up

with another prospective case-control study of young girls with distal forearm fractures and demonstrated that history of previous fractures, low total body BMD, and high body weight each independently raises the risk of new fractures at any skeletal site with risk ratios of 9.4-13 in those having more two or more of these risk factors (Goulding et al 2000). The risk of new fracture doubled with each standard deviation decrease in BMD. This study however, did not have any information regarding the predictive nature of family history, risk taking behavior, nutrition or activity.

Ferrari et al conducted a prospective cohort study of 125 healthy girls over 8.5 years and observed that amongst the 42 subjects reporting 58 fractures, total skeletal BMC and vertebral bone size at pubertal maturity were decreased (Ferrari et al 2006). The authors proposed that a history of childhood fractures might indicate low peak bone mass acquisition and ongoing skeletal fragility. Furthermore, the study reported strong correlation for BMC throughout puberty as well as strong BMC correlations between mature daughters and their mothers. This may suggest a component of heritability for bone mass, however, the influence of environmental factors such as diet, activity levels, smoking and poverty may also be similar between family members and may also have influenced BMC correlations here.

Many studies demonstrate the ability of bone density to predict fractures, especially fragility fractures (those caused by minor trauma) (Lunt et al 1997; Marshall et al 1996). The relative risk of a fracture increases by 50-150 % for each standard deviation of bone density below the age-matched mean (Marshall et al 1996). The risks vary depending on the populations studied and on the technique of measuring the bone density. However, in adults, BMD alone can predict fractures with a detection rate of only 30 – 50% and a false positive rate of about 15%.

Measurements of BMD can predict fracture risk but cannot identify individuals who will have a fracture (McCreadie, & Goldstein 2000).

In children, although an increasing number of studies have demonstrated an association between low bone mass and increased fracture risk (Boot et al 2010; Clark et al 2006a; Clark et al 2006b; Flynn et al 2007; Michałus et al 2008), the associations differ when compared to the associations described between adult fracture and bone mass (Bogunovic et al 2009). As children are actively growing and peak bone mass has not yet fully been achieved, reference standards and scoring systems used to assess BMD differ from those used in adults (Z-score in children and T-score in adults) (Bogunovic et al 2009). Historically, standardized norms for children have not been easily determined or largely available, although more recent reports may have begun to address this issue in part (Gordon et al 2008; Kalkwarf et al 2007). Pediatric bone is naturally less dense than adult bone (Rauch et al 2001) and so densitometers calibrated using adult parameters may underestimate pediatric BMD (Bogunovic et al 2009). Modified software to correct for these and other differences has been designed but is not yet universally used, resulting in inaccurate BMD estimates for some children (Bogunovic et al 2009). Furthermore, childhood comparisons should only be made with healthy subjects of the same age, sex and ethnicity (Bianchi et al 2010) but with a paucity of data, this is difficult to achieve for some children. Other growth related issues such as mechanisms of skeletal growth, body size, bone size, skeletal age vs. chronological age, pubertal development and the influence of hormones during growth, further compound difficulties with interpretation of pediatric BMD (Bogunovic et al 2009; Bianchi et al 2010). Thus clarity around our understanding as to whether low BMD in children can accurately predict fracture risk in children is still evolving.

Chapter 1:5 Fracture at a young age or prior fracture is a predictor of future fracture

A history of prior fractures appears to be an important risk factor for new fractures. One pivotal study in young girls has determined that the history of a previous forearm fracture is a risk factor for future fractures that is independent of BMD (Goulding et al 2000). Goulding, in a longitudinal birth cohort of 601 children, demonstrated that incidence rates of subsequent fractures to age 18 years increased with increasing numbers of prior fractures. When adjusted for age and sex, hazard ratios for further fracture were 1.90 (95% CI 1.51 – 2.39) after first fracture and 3.04 (95% CI 2.23 – 4.15) after a second fracture (Goulding et al 2005).

Based on observed associations between early childhood fractures with later childhood fractures, researchers have theorized that a particular sub-group of children may have a propensity to fracture and that these children may have higher risk of repeat fractures throughout childhood (Yeh et al 2006; Tiderius et al 1999; Landin 1983; Jones et al 2002; Goulding et al 2000; Goulding et al 2005; Goulding et al 2005; Cooper et al 2004). Landin's study of 18 thousand childhood fractures revealed that prior fracture and early age of initial fracture were important risk factors for future fracture (Landin 1983; Landin 1997). Yeh demonstrated that of children suffering multiple fractures over childhood, 84% experienced their first fracture before the teenage years. Fifty percent of children experiencing first fracture before 13 years of age and only 20% of children experiencing first fracture as a teenager had further fractures (Yeh et al 2006). In a cohort study of children aged 5-19 years of age experiencing two or more fractures, Goulding demonstrated that children with early age of first fracture (less than 10 years) had higher rates of fracture than those who sustained fractures later (Goulding et al 2005). These results suggest that children who experience fractures at a young age may have some underlying features which put them at risk for future fractures as compared to teenagers with first time

fractures who seem to fracture as a once off chance event during the somewhat normally vulnerable adolescent growth spurt.

Potential reasons for these observations across multiple studies are currently unclear but possibilities are variable. The features that contribute to subsequent fractures are possibly the same features that contributed to the first fracture. Increased fracture risk could reflect weakness or differences in bone architecture, density or mineralization as has been previously described. Alternately or in concert, other genetic factors and/or environmental influences may play significant roles. Currently, clear explanations for these observed associations are lacking and further examination of this topic is warranted.

Chapter 1:6 Role of trauma and biomechanics

In simple terms, for a fracture to occur, there must be an imbalance between bone strength and force on the bone (Currey 2005; Brandi 2009; McCreadie, & Goldstein 2000). Trauma depends on factors related to falling and to the force of the impact. For example, bones will break more easily when subjected to torque than compression (McCreadie, & Goldstein 2000). Some studies suggest that direction of traumatic impact is a greater risk factor for fracture than lower bone density (Davidson et al 2003; Silva 2007). The force applied must exceed bone strength in order for a fracture to occur. Most children incur fracture during normal play or sport with less than 10% of all childhood fractures involving major trauma or fall from greater than 3 meters (Clark et al 2008a; Clark et al 2008b; Hagino et al 2000; Landin 1983; Landin 1997; Rauch et al 2001). Factors affecting trauma and the force of the traumatic event are difficult to assess and quantify and the literature on this topic is minimal.

What we know of biomechanics suggests that the risk of fracture is dependent on the character of the imposed load (magnitude, rate and direction), the geometry of the bone, its macro and micro architecture and the distribution and quality of its material properties (McCreadie, & Goldstein 2000). The force applied to the bone is influenced by padding (artificial or body fat), the distribution of mass and the direction of the fall (Currey 2005; Davidson et al 2003; Silva 2007).

It appears that muscle forces exert greater force on bones than gravitational forces secondary to weight. The 'mechanostat' describes the process of an individualized set point by which optimal bone architecture and density is attained in response to exercise and an ideal minimum magnitude of applied load (Frost 1982; Skerry 2006). Increase and decrease in magnitude of force would result in bone formation and bone desorption respectively. However peak magnitude is only one of a varied and complex set of influences on the skeletal response to strain stimulus, which also varies by skeletal site (Skerry 2006). Other factors include gender, specific responses to load bearing on bone, genetics, age, nutrition, disease and toxin exposure and degree of trauma. Bones adapt to muscle forces in the ongoing remodeling process rather than by loads imposed by extra fat mass.

Obesity, with a mixed heritable and/or acquired etiology may increase risk of fractures (Davidson et al 2003; Goulding et al 2000; Goulding et al 2001; Goulding et al 2005; Skaggs et al 2001). Overweight children have a higher risk of fracture due to the larger force from increased body mass that is placed on the bone during a fall (Currey 2003; Davidson et al 2003; Goulding et al 1998; Goulding et al 2000; Goulding et al 2001; Goulding et al 2005). High adiposity was prospectively identified as an independent risk factor for forearm fracture (Goulding et al 2000). BMC is reduced in comparison to body weight in obese children and since

bone composition changes in response to muscle forces rather than extra fat mass the disproportionate gain in extra fat mass over lean muscle mass, lends to increased risk of fracture in obese children (Farr et al 2010; Goulding et al 2000; Petit et al 2005). Another important feature in predisposition to fracture may be secondary to exercise avoidance and resultant in-coordination, impaired musculoskeletal development and carrying of a higher inert fat mass (Goulding et al 2003). Obesity is also associated with low levels of growth hormone and higher corticosteroid levels, which may also elevate fracture risk (Baroncelli et al 2002; Helenius et al 2006).

Chapter 1:7 Environmental influences on fracture risk

Research into a possible link between fracture risk and nutritional deficiencies is developing. A randomized controlled trial (RCT) of calcium supplementation in girls has provided evidence that sub-optimal calcium may increase fracture risk and calcium supplementation decreases rate of fracture (Matkovic et al 2005). Vitamin D insufficiency, due to its effect on optimal calcium absorption and subsequent bone mineralization, has been associated with low bone density in children (Cooper et al 2005; Ferrari et al 1998; Javaid et al 2006; Mahon et al 2009) however the link to childhood fractures has not yet been studied. Vitamin D supplementation during infancy results in a greater BMD at the proximal femur and radius by age 7 (Zamora et al 1999). A meta- analysis of RCTs to assess the effectiveness of vitamin D supplementation in preventing hip and non-vertebral fractures in people older than sixty years found that oral supplementation of 800 IU/d vitamin D appears to reduce the risk of these fractures (Bergman et al 2010; Bischoff-Ferrari et al 2009).

Evidence that chronic milk avoidance increases fracture risk exists. Milk avoiders are shorter, have lower bone mass, smaller skeletons and a 3-fold greater fracture risk than age and

sex-matched controls (Black et al 2002; Henderson, & Hayes 1994; Infante, & Tormo 2000; Jensen et al 2004; Rockell et al 2005; Stallings 1997). Young adults who avoided milk during growth have been shown to have lower peak bone mass and women who drank milk less than once per week in childhood had higher rates of osteoporotic fractures than those drinking daily (Di Stefano et al 2002; Kalkwarf et al 2003; Kanis et al 2005). Interestingly children who have high rates of adverse symptoms associated with milk such as rhinitis, eczema and gastrointestinal discomfort tend to be overrepresented amongst children with fractures.

Caffeine containing soft drinks are hypercalciuric, as are foods containing salt or sulfur amino acids and may affect bone mineralization through calcium losses. Choice of nutrient poor soft drinks amongst children, displaces the opportunity for milk and increases risk of obesity. A few studies confirm increased fracture rates or decreased BMD amongst children drinking large amounts of carbonated drinks (Ma, & Jones 2004; McGartland et al 2003; Tucker et al 2006; Whiting et al 2004; Wyshak 2000).

Reviews of patients with eating disorders indicate that calorie restriction and low estrogen status results in a doubling of the risk of fracture when compared to controls (Vestergaard et al 2002; Vestergaard et al 2003) and previous studies have demonstrated low bone mass in such patients (Grinspoon et al 2000; Soyka et al 1999).

Jones et al. found an association between sunlight exposure and bone mass at all sites with a stronger association in girls (Jones, & Dwyer 1998). This is likely secondary to increased photosynthesis of vitamin D as well as increased physical activity outdoors. Cigarette smoking raises the risk of fractures somewhat in adolescents with a relative risk of 1.43(95%CI 1.05-1)

(Jones et al 2004) and in adults with a relative risk of 1.26(95% CI 1.12-1.42) (Vestergaard, & Mosekilde 2003).

Skeletal response to the bone forming benefits of exercise are greatest during childhood growth and adult bone mass is in large part, laid down by age 17 (Foley et al 2008). Low sports participation with subsequent failure to maximize peak bone mass may play a role in fracture risk. Small pediatric RCTs have demonstrated short-term gains in bone mass secondary to weight- bearing exercises although it is uncertain as to whether the benefits are long-standing (Bradney et al 1998; Eliakim, & Beyth 2003; Fuchs et al 2001; Fuchs, & Snow 2002; Gunter et al 2008; Heinonen et al 2000; Matthews et al 2006b; Matthews et al 2006a; McKay et al 2000; Rautava et al 2007; Clark et al 2008b) However, vigorous exercise has been shown to confer an increased risk of fracture (OR 2.06; 95% CI 1.21-1.76) despite being associated with higher BMD and bone size (Clark et al 2008b), presumably secondary to increased opportunity for a traumatic event(Ma, & Jones 2004; Lyons et al 1999; Khosla et al 2003, Clark et al 2008b).

Increased risk-taking behavior leading to higher fracture rates may be environmental (learned through observation or family or peers) or inherited through conditions such as attention deficit hyperactivity impulsivity disorders (Barkley 2002; Bruce et al 2007; Brudvik, & Hove 2003; Ma, & Jones 2004; McLoughlin et al 2007; Swensen et al 2004; Uslu, & Uslu 2008; Uslu et al 2007). High-risk activities such as involvement in particular sports or criminal lifestyles are also associated with increased risk of fracture (Goulding 2007a; Landin 1983; Landin 1997). Use of performance enhancing drugs may alter bone metabolism, cause short stature and changes in muscle integrity that can predispose to injury (Calfee, & Fadale 2006).

Chapter 1:8 Children with chronic disease or certain monogenic traits are at increased risk for fractures

Children with genetic or chronic disease are at increased fracture risk secondary to under-nutrition, and poor nutrient absorption, inactivity, impulsive activity, muscle weakness, in-coordination and falls, medications or radiotherapy (Henderson, & Hayes 1994; Henderson et al 2002; Larson, & Henderson 2000; McDonald et al 2002; Tinkle, & Wenstrup 2005; van Staa et al 2003; van Staa et al 2004; Vestergaard et al 2002). Medications increasing fracture risk are numerous and include immunosuppressive and chemotherapy, oral corticosteroids, warfarin and anti-epileptic medications (Boot et al 1997; Sheth, & Hermann 2008; Sheth et al 2008; Goulding 2007b; van Staa et al 2003; van Staa et al 2004). Several single gene disorders with a propensity to multiple fractures exist, and many of them can have a normal phenotype. These include Osteogenesis Imperfecta, hypophosphatasia, hyperphosphatasia, hypophosphatemic rickets, and congenital insensitivity to pain with anhydrosis (Tinkle, & Wenstrup 2005).

Chapter 1:9 Common genetic polymorphisms may increase fracture risk

Genes that appear to be important in the regulation of bone mass and in the process of osteoporosis are either those coding for receptors or enzymes. Multiple polymorphisms of the estrogen receptors (ERs), ER alpha and ER beta, have been reported and may provide opportunities for pharmacogenomic interventions (Langdahl et al 2000b; Thijssen 2006). Androgen receptor polymorphisms have also been reported and some polymorphisms are associated with low bone mass. The role of the vitamin D receptor and the vitamin D endocrine system has been recognized in rare disease such as rickets, immune disorders and cancer. More subtle polymorphisms are seen more frequently but their functional consequences in terms of skeletal metabolism are not well understood (Garnero et al 1995; Sainz et al 1997).

Genes involved in hormone synthesis, specifically the cytochrome P450 (CYP) genes, CYP19 (responsible for estrone and estradiol production) and CYP17 (involved in 17-alpha-hydroxylase and 17,20- lyase) have been reviewed. Although animal studies of aromatase knock out mice demonstrate decreased BMD, human studies examining a link between gene polymorphisms and decreased BMD are variable (Riancho et al 2005; Salmen et al 2003; Sharp et al 2004; Somner et al 2004; Tofteng et al 2004). The ubiquitous collagen type 1 protein is preferentially formed in the bone and polymorphisms have been associated with a modest reduction in BMD and significant increase in osteoporotic fracture (Nguyen et al 2005; Mann, & Ralston 2003; Uitterlinden et al 1998).

Chapter 1:10 Fracture risk as a complex trait

We know that children fracture and so suspicion that genetic determinants affect children in terms of fracture morbidity is reasonable. Genetics can influence the geometry, material properties, architecture of bone or the propensity for an individual to alter these features in response to the environment or underlying physiological conditions. It is conceivable that multiple alleles at multiple loci within the genome interact along with environmental factors, possibly at different times in development, to produce vulnerability to fracture. Epigenetic chance factors might act during early development to influence vulnerability to fracture over the lifespan. Genetic factors might not be independent and one set of common genes may contribute to variation in phenotype and liability to fracture. Apart from the contribution of individual genes, gene-gene and gene-non-gene factor interactions may work to convert vulnerability into actual fracture outcomes.

However, despite the growing understanding of ties between bone traits and genetic polymorphisms, linkages are inconsistent and explain only a small share of the trait variance

(Langdahl et al 2000a; Langdahl et al 2000b; Thijssen 2006). Clinically, the identification of genotype-specific individuals at risk of fracture or evidence of successful interventions for genotype specific individuals at risk of fracture has not been strong (Seeman 2002). This may reflect that genetics might only play a small part in the complex issue of liability to fracture.

In addition, complex genetic factors other than those related to bone strength, may contribute to the risk of fracture. These factors may be influenced by genetics, the environment or may otherwise cluster in families and include such factors as risk-taking behaviors, nutrition, activity levels, type of sports participation, muscle weakness, postural instability and hormonal milieu amongst others. For example, two cohorts of children with fractures were shown to have high rates of impulsive – hyperactive behavioral problems (Uslu, & Uslu 2008; Uslu et al 2007). Ma demonstrated that adolescents displaying high risk-taking attitudes have a higher association of hand fractures than control subjects (Ma, & Jones 2004). Conduct problems and hyperactivity appear to be associated with risk-taking and making simple errors such as clumsiness or absent-mindedness and history of childhood injury (Rowe, & Maughan 2009). A large cohort of 6-19 year old children with ADHD were shown to be at increased risk for both minor and serious injuries (Bruce et al 2007). Familial aggregation of similar complex parameters could contribute to the risk of fractures. In addition, other chronic diseases with complex genetic contributions, such as inflammatory bowel disease, can also contribute to increased fracture risk but for complex reasons (Boot et al 1998; Kluge et al 2007). The relative contributions of genetics, the environment and complex aggregation of familial traits to fracture events is currently unclear.

Chapter 1:11 Family history as a specific risk factor for fracture

Despite what is now known about metabolic bone disease, little is known about fracture risks especially in children and within families (Zmuda et al 1999). Previous studies in adults

assessing contribution of family history to osteoporotic fracture suggest that a family history of osteoporotic fracture confers a significant increase in risk of osteoporotic fracture for a relative (Cummings et al 1993; Kanis et al 2004; Nguyen, & Eisman 2000). Kanis' meta-analysis revealed that a parental history of fracture imparted an increased risk of fracture that was independent of BMD and was higher when combined with sibling history for some fracture types (Kanis et al 2004).

From the pediatric literature only one cross sectional questionnaire has explored the question of fracture rates in relatives of children with fractures. Konstantyowicz questioned 1,246 adolescents aged 16-20 years, and gathered information pertaining to fracture history, family history, diet and exercise and body mass index. He found that among subjects with multiple fractures, 52% reported fractures in at least one family member as compared to those children who had never experienced a fracture. The authors also noted that fractures in mothers and siblings accounted for 44% of the variance in adolescents' fractures. (Konstantynowicz et al 2005)

The question as to whether a family history of fracture confers an increased risk of fracture for children deserves more complete exploration. If present, understanding both the magnitude of this risk and the etiology of this risk is important. If a family history of fractures proves to be a risk factor for fractures in a child, perhaps preventative interventions in childhood, for those identified to be at risk, would have considerable implications for health care services for children. Also, if proven to be a risk factor, identifying a family history of fractures is easy and inexpensive. Traditional methods employed to evaluate genetic contribution to a multifactorial disease include determining familial aggregation through population based studies, discriminating among environmental or genetic factors via concordance in monozygotic versus

dizygotic twins and finally identifying specific genetic variants via linkage or association studies. In this study we attempt to quantitate the familial aggregation of childhood fractures. It is critical to document that a disease has a high burden of familial aggregation prior to investing time and resources into investigating the specific genetic variants.

Chapter 1:12 Proposed research and thesis objectives

The primary objectives of the study are as follows:

(1) To determine if high familial aggregation of fractures exists, by assessing the prevalence of fractures among first degree relatives of cases and controls, through construction and screening of genetic pedigrees in order to obtain the odds ratios of fracture risks within the family.

(2) To explore the relative role of selected environmental factors, particularly nutrition and activity levels in determination of fracture risk.

(3) To generate a reasonable hypothesis to describe any identified relationships.

CHAPTER 2: Materials and Methods

Chapter 2:1 Subject selection

Study Design: Case control study with preliminary background review of injury database.

Study Population: Healthy children, 0- 16 years of age, attending the Janeway pediatric emergency department (PED), living in the province of Newfoundland and Labrador.

Study Timeframe: July & August in each year of 2002- 2004.

Inclusion Criteria:

1. Children aged 0 - 16 yrs.
2. Cases: Clinically documented fracture.
3. Controls: No current fracture or history of fracture.

Exclusion Criteria:

1. A chronic disease that may predispose to fracture:

- Endocrine: Hyper/Hypothyroidism, hyperparathyroidism, diabetes, growth hormone deficiency, osteoporosis, hypogonadism.
- Gastrointestinal: Cystic fibrosis, liver disease, celiac disease, inflammatory bowel disease.
- Neurological: Spina bifida, epilepsy, immobilization, cerebral palsy, neuromuscular disease.
- Other: Collagen vascular, asthma, chronic renal disease, malignancy, transplants, metabolic acidosis.

2. Medications: oral contraceptive, steroids, fluoride, phosphates, calcium, vitamin D.

Chapter 2:2 Sampling methods

Background Review: In order to determine feasibility of this study, and in order to describe the basic context of fractures in the pediatric referral center for Newfoundland and Labrador, a background review of fracture epidemiology at the emergency department was done. Injury data, over 10-year period, were obtained from the database of the Canadian Hospitals Injury Reporting and Prevention Program (CHIRPP), Public Health Agency of Canada (2002). Summary statistics were calculated.

Case-Control Study:

Patients were recruited from the pediatric emergency department (PED) at the Janeway Child Health Center, St. John's, Newfoundland and Labrador. The PED has an annual census of 34,000 emergency visits, is the acute care center for St. John's (metropolitan area census of 200,00) and is the only pediatric referral centre for the entire province of Newfoundland and Labrador (census 500,000). Any child meeting inclusion criteria who presented to the emergency department with a fracture, as documented by x-ray was asked to partake in the study as a case. All consecutive children with fractures were approached to participate whether or not the fracture was considered mild, moderate or severe by mechanism or outcome.

Controls were any consecutive child meeting inclusion criteria without history of fracture or current fracture attending the pediatric emergency department for an unrelated

matter. Potential study subjects were identified by clinical nurses who notified a research assistant. Potential subjects were then informed of the study, asked to sign consent and given an information package. Study subjects were asked to fill out a case report form (Appendix A) in the patient assessment room, while awaiting further management for the chief complaint. The research assistant remained available to answer any questions or to assist with filling out the form if needed but the forms were largely self-administered. The case report form consisted of a general medical history and a series of questions relating to fracture histories of family members and environmental aspects such as diet and exercise. Children had assistance from their parents to complete this form. The parents of both cases and controls were also administered the parent case- report form (Appendix B). This also consisted of a general medical history, questions relating to fracture histories of family members and environmental aspects such as diet and exercise. The parent filling out the form could call the other parent if uncertain of details regarding that parents' fracture history, if needed. The identity of the person who filled out the form (mother or father) was recorded. The research assistant then extracted the data, entered it into an Excel spread sheet and constructed pedigree diagrams of each family to aid assessment of odds ratio calculations (Fig 3-1).

Measurement tools:

The report forms (Appendices A & B) were designed by primary researcher and was based largely on nutritional estimates from the Osteoporosis Society of Canada

(Osteoporosis Society of Canada 1995), the American Academy of Pediatrics Committee on Nutrition (Committee on Nutrition 1999) and the NIH (National Institutes of Health 2002). The report form contained information on diet, activity, sleep, sunlight exposure and standard medical information. The force under which the fracture was sustained was estimated on a 3-point scale from a retrospective description of events (Appendix C). The instrument was considered appropriate in terms of face validity after considering the feedback from five parents in the emergency department and two other adults with a non-medical background, who had reviewed the questionnaires, via pilot –testing, prior to the study initiation. Content validity was improved based on the reviews of a general pediatrician, two pediatric endocrinologists, an internal medicine specialist, a geneticist and two senior pediatrics residents. Other attempts to establish other types of validity, such as construct validity, were not made.

Ethical considerations: Ethical approval by the Human Investigations Committee at Memorial University of Newfoundland and Health Care Corporation of St. John's was granted. Signed informed consent was obtained from all study subjects (Appendix D) and subjects were reassured that they could leave the study at any time without compromise to routine care. Study design and implementation met all the guidelines of the Tri-Council's policy statement of August 1998 (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada 1998). Patient confidentiality was

strictly protected. Subjects and parents were assigned a unique identifier and all information and results pertaining to each subject were recorded under this number. Names were not used and only the principal investigator knew which number was associated with each subject or parent. All documentation was locked in a secure cabinet, kept confidential for the length of the study and kept for duration of seven years.

Chapter 2:3 Data handling

Sample size determination: We assumed a baseline childhood fracture rate of 0.3 for a parent based on previous epidemiological data that report that at least 27% of females report a fracture (Tiderius et al 1999). We then postulated that cases with childhood fractures would have a fracture risk that is at least 1.8x greater than baseline (56%). As a result N-Query Advisor 4.0 was used to compute the sample size using the assumptions of 0.3-fracture rate among a parent of a control and 0.56-fracture rate among at a parent of a case. Then the alpha was set at 0.05, and power at 80%.

Assuming that controls would have a probability of exposure of 0.3 and cases would have a probability of exposure of 0.56, we calculated that we would require 64 patients of each in order to detect a statistically significant difference between the groups using an alpha level of 0.05 and a power of 80%. Expecting worst case-scenario dropouts of around 40% (incomplete questionnaires for crucial data such as family history or surveys not returned), we attempted to recruit at least 90 patients in each group to ensure that we would meet our sample size for calculable data. Further details include:

Formula for standard chi-square:

$$n = \frac{\left[z_{1-\frac{\alpha}{2}}\sqrt{2\bar{\pi}(1-\bar{\pi})} + z_{1-\beta}\sqrt{\pi_1(1-\pi_1)+\pi_2(1-\pi_2)}\right]^2}{(\pi_1-\pi_2)^2}$$

The following formula was then used to adjust for continuity correction:

$$n' = \frac{n}{4}\left[\sqrt{1+\frac{4}{n|\pi_1-\pi_2|}}\right]^2$$

Where π_1 and π_2 are the expected proportions in the two groups (0.3 and 0.56 in this case) and $\bar{\pi}$ is their mean (0.43 in this case). z represents the respective quantile on the standard normal curve, and alpha and beta are the probabilities of type I and II error respectively.

Statistical analysis: Data was extracted from report forms and entered into MS Access database by a research assistant. Analysis was done in SAS, version 9.1. Univariate analysis was used to compare the two groups with respect to demographics as well as genetic and environmental risk factors for fractures. Continuous variables were compared using the student t-test while the categorical variables were assessed using a contingency table with chi-squared tests. For categorical variables, if the expected frequencies in any cell were less than 5, Fisher's exact test was used. The Kruskall-Wallis test was used for ordinal data. Multivariate logistic regression was used to evaluate multiple variables and their effect on probability of fracture. The odds ratios or risk ratios of fracturing were calculated. As this was an exploratory study, no corrections were made for multiple comparisons. Differences were considered statistically significant at the p value <0.05.

The normal approximation to the binomial distribution was used to obtain standard deviations of the observed proportions. We tested if the proportions of probands with maternal versus paternal history of fractures were different from 0.5. The variables for the expression of maternal and paternal fractures were compared using a t-test for continuous variables and Fisher's exact test for categorical variables.

CHAPTER 3: Results

Chapter 3:1 Background chart review

A review of pediatric emergency department injury records over a ten-year period (1991- 2000) revealed that of the 61,762 records reviewed, 10,194 of the diagnoses were fractures. Therefore, of the patients treated at the ED for injury, 17 % suffered a fracture. Given an annual census of 34,000 visits, roughly 3 % of total visits to the pediatric emergency department were for fractures.

From the records reviewed, males sustained these fractures twice as often as females. The most commonly fractured body parts were the forearm (24%), finger/thumb (17.1%), hand (9.8%), clavicle (6.5%) and lower leg (6.7%). The percentage of fractures treated per month ranged from 6.6% in December to 10.1% in June, July and August. Two percent of fractures required advice only as management. At least 90% required treatment with follow up and 7 % required admission to hospital.

Chapter 3:2 Case control study

Of the 184 subjects initially approached for recruitment, 165 (90%) returned the questionnaire and 150 (82%) were used in the analysis (Figure 3-1). Fifteen questionnaires were either illegible (2 cases) or were missing most of the data including key information such as family history or environmental features (8 controls and 5 cases) and so could not be used. Data was obtained from 79 cases (mean age 10 years) and 71 controls (mean age 8.8 years). Boys made up 62% of the fracture group and 53% of the control group. The ethnicity of both groups was 90% Caucasian. The two groups did not differ significantly in age of parents, with mothers averaging around 36 years and fathers

closer to 39 years on average. The general characteristics of the study subjects are shown in Table 3-1.

In terms of lifetime fractures, of the 79 cases, 76% reported to having had one fracture; 16% reported to having had two fractures and 6.3 % reported to having had 3 or more fractures. The maximum number of fractures reported by one person was 6. Twenty-four percent (n=19) reported having had multiple fractures and boys made up a larger proportion of that group. More boys than girls had fractures (62% vs. 38 %, p =0.32), while the proportion of boys and girls having had multiple fractures was 68 % vs. 32 % ($p< 0.59$). Ninety percent of boys and 84% girls sustained their fracture under an estimated moderate force and the remainder fractured under an estimated mild force. No children in this study sustained fractures under severe force. The most common fracture site, in both sexes, was the forearm, accounting for over 47 % of all fractures. Fingers and legs followed in terms of frequency and other locations included the clavicle, elbow, foot, hand, knee and skull (Table 3-2).

Environmental factors

When examining environmental or baseline risk factors for fractures (Table 3-3), t- test and regression analysis revealed that cases and controls did not differ with respect to average activity, sleep, sunlight, calcium, cola consumption, birth weight or prematurity. When comparing boys vs. girls in the fracture group, on average, boys were older than girls (11 yrs vs. 9 yrs; p=0.01) but otherwise environmental or baseline risk

factors did not differ between the two (Table 3-4). None of these factors were independently associated with fracture occurrence.

Family history of fractures (Tables 3-5 - 3-7; Figs 3-2 - 3-4)

The occurrence of fractures amongst parents differed between cases and controls (Table 3-5 & Figure 3-2). Thirty- nine percent of the mothers of cases fractured vs. 23 % of the mothers of controls. If a child's mother had fractured the OR (Odds Ratio) for fracture for that child was 2.2 (95% CI 1.09, 4.52); p=0.036 (Table 3-6). Fifty – seven percent of the fathers of cases fractured vs. 39 % of the fathers of controls. If a child's father had fractured the OR for fracture for that child was 2.03 (95% CI 1.06, 3.9); p=0.035 (Table 3-6).

Of the cases, 48% parents (31 mothers and 45 fathers) had sustained fractures as compared to 31 % parents (16 mothers and 28 fathers) in the control group; p=0.007 (Table 3-5). Cases were more likely than controls to have a parent with a fracture (RR 1.37, 95 % CI 1.00-1.89) (Table 3-7).

Twenty five percent of the cases group had fractures in both parents whereas only eight percent of the control group had fractures in both parents. If both parents had sustained a fracture the OR for fracture for that child was 3.7 (95% CI 1.1, 9.48); p= 0.009. Seventy one percent of the cases group had a fracture in either parent vs. 53 % of the control group. If either parent had sustained a fracture the OR for fracture for that child was 2.1 (95% CI 1.0, 4.13); p= 0.042. Only 29 % of the cases group had neither

parent experience a fracture vs. 46 % of the control group resulting in an OR for fracture for a child of 0.5 (95% CI 0.24- 0.92); p = 0.042 if neither parent had experienced a fracture (Table 3-6).

When cases were subdivided into single and multiple fracture groups some trends towards increased proportions were seen in the multiple fracture group (Table 3-5). Fifty –eight percent of the mothers of multiple fracture children vs. 33 % of the mothers of single fracture children experienced fractures. Eighty four percent of the multiple fracture group had either parent fracture vs. 67 % of the single fracture group. Also of note, the prevalence of neither parent fracturing was higher in the single fracture group (38%) as compared to the multiple fracture group (16%). In contradistinction to these, fathers with fractures, were more heavily represented in the single fracture group as compared to the multiple fracture group (62% vs. 42%).

When considering other first-degree relatives (siblings), some basic proportions of fracture burden between groups were calculated (Table 3-7, Figure 3-3). The number of siblings in the cases and control groups were similar (average number siblings 1.2 vs. 1.3; p = 0.59). However, 32% of the siblings in the cases group had experienced fractures whereas only 15 % of the siblings of the control group had experience fractures. Cases were twice as likely as controls to have a sibling with a fracture (RR 2.0; 95% CI 1.09, 3.68). Again, the total number of first-degree relatives experiencing fracture was doubled in the cases group as compared to the control group (42% vs. 24 %) and cases were 1.5 times as likely than controls to have a first degree relative with a fracture (RR 1.50; 95 %

CI 1.13,1.99). Examining families in whom all first-degree members had experience fractures, 13 % were found in the cases group compared to only 4 % in the control group (Table 3-7; Figure 3-4). Examination of case subgroups (single vs. multiple) did not reveal any particular trends (Table 3-7).

Chapter 3:3 Tables

Table 3-1. Baseline characteristics for cases and controls

	Controls (n=71)	Cases (n=79)	p-value
Average Age (years)	8.8	10	0.05
Male Sex (%)	53	62	0.32
Ethnicity % Caucasian	89	90	----
Average # siblings	1.2	1.3	0.59
Average Lifetime Fractures	0	1.4	-----
Average Mothers Age	36.6	36.8	0.86
Average Fathers Age	38.1	39.5	0.23

Table 3-2. Cases fracture sites; number (%)

Mean Values	Boys (n=49)	Girls (n=30)	All (n=79)
Upper Limb			
Forearm (Any of Radius, Ulna)	18 (37)	19 (63)	37(47)
Finger	7 (14)	1 (3)	8(10)
Clavicle	6 (12)	1 (3)	7 (9)
Elbow (Distal Humerus)	4 (8.1)	2 (7)	6 (8)
Hand	2 (4.0)	0 (0)	2 (3)
Lower Limb			
Leg (Any of Femur, Tibia, Fibula)	5 (10.2)	7(23)	12 (15)
Foot	4 (8)	0 (0)	4 (5)
Knee (Tibial tubercle secondary to Patellar dislocation)	2 (4)	0 (0)	2 (3)
Other			
Skull	1 (2)	0 (0)	1 (1)
Fracture Frequency			
One fracture only	36 (73)	24 (80)	60 (76)
Two fractures	8 (16)	5 (17)	13 (16)
Three fractures	4 (8)	1 (3)	5 (6.3)
Multiple fractures	12 (25)	6 (20)	19 (24)
Fracture burden*	1.4 (NA)	1.2 (NA)	1.35(NA)

* Calculated as total number of fractures/total subjects. NA listed in brackets to emphasize that % calculation does not apply here.

Table 3-3. Risk factor comparisons for cases and controls

	Controls	Cases	p-value
Average Activity (hours/day)	9.6	10	0.82
Average Sleep (hours/day)	9.0	9.4	0.09
Average Sunlight (hours/week)	8.3	8.0	0.67
Average Calcium (mg/day)	1587	1510	0.7
Average Cola (drink/day)	0.3	0.4	0.28
Average Birth Weight (kg)	3.5	3.4	0.4
Prematurity (%)	14	15	1.00

Table 3-4. Cases comparisons girls vs. boys

Mean Values	Boys	Girls	p-value
Average Age (years)	11	9	0.01
Average Activity (hours/day)	11.3	7.8	0.19
Average Sleep (hours/day)	9.2	9.7	0.09
Average Sunlight (hours/week)	8	8	0.36
Average Calcium (mg/day)	1424	1849	0.18
Birth Weight (kg)	3.5	3.4	0.54
Total # siblings (n)	73	34	0.03
Mothers Age (years)	40	38	0.12

Table 3-5. Prevalence of fractures in parents (fractured/non-fractured members)

Family Members	Controls n=71 (%)	Single fractures n=60 (%)	Multiple Fractures n=19 (%)	Cases n=79 (%)
Mothers	16 /71 (23)	20 /60 (33)	11/19 (58)	31/ 79 (39)
Fathers	28/71 (39)	37/60 (62)	8/19 (42)	45 / 79 (57)
Both Parent Fractured	6/71 (8)	17/60 (28)	3/19 (16)	20/79 (25)
Either parent fractured	38/71(53)	40/60 (67)	16/19 (84)	56/ 79 (71)
Neither parent fractured	33/71(46)	20/60 (33)	3/19 (16)	23/79 (29)

Table 3-6. Odds ratios for fracture based on parental history of fracture

	If mother Fractured	If father Fractured	If both parents Fractured	If either parent Fractured	If neither parent Fractured
Odds Ratios of fracture for Child	2.2	2.03	3.7	2.1	0.5
95 % CI	1.09–4.52	1.06–3.9	1.14–9.48	1.08–4.13	0.24–0.92
p-value	0.036	0.035	0.009	0.042	0.042

Table 3-7. Prevalence of fractures in first-degree family members (fractured/non-fractures members. Fracture burden in each group (Ratio, %)

	Controls (n=71)	Single (n=60)	Multiple (n=19)	Cases (n=79)	RR* (95% CI)
Total Sisters	5/42(12)	15/40 (38)	1/11(9)	16/51 (31)	2.24 (0.88, 5.70) (p=0.09)
Total Brothers	7/45 (16)	10/37 (27)	7/15 (47)	17/52 (33)	1.83 (0.82, 4.09) (p=0.14)
Total Siblings	12/87 (15)	25/77 (32)	8/26 (31)	33/103 (32)	2.00 (1.09, 3.68) (p=0.026)
Total parents	44/142(31)	57/120 (48)	19/38 (50)	76/158 (48)	1.37 (1.00, 1.89) (p=0.055)
Total first-degree relatives	56/229 (24)	82/197 (42)	27/64 (42)	109 /261 (42)	1.50 (1.13, 1.99) (p=0.005)
All first-degree members fractured (number of individuals)	3/71(4)	8/60 (13)	2/19 (11)	10/79 (13)	N/A

*Risk Ratio for Controls vs. Cases were calculated

Chapter 3:4 Figures

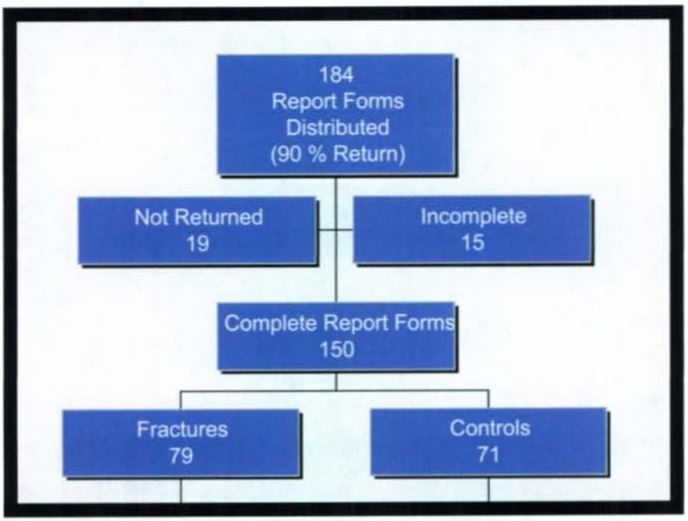

Figure 3-1. Overview of enrollment, methods and results.

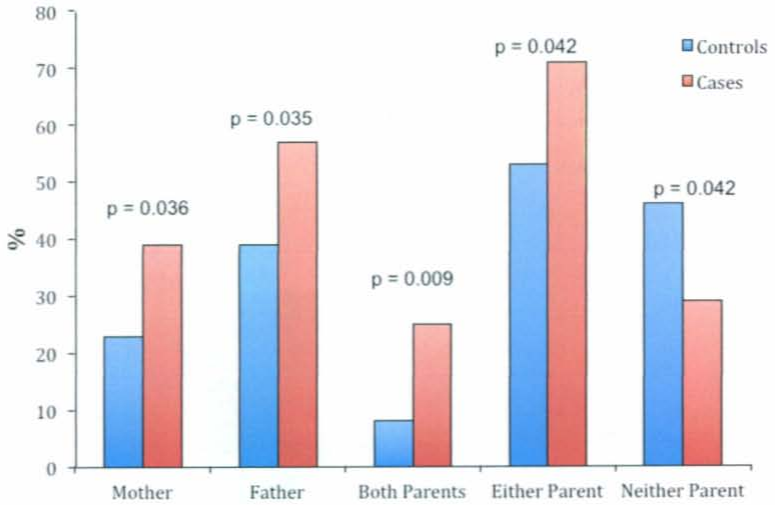

Figure 3-2. Proportion of parents with fractures for cases vs. controls. The p value is testing the significance of the difference between the cases and the control groups for the occurance of fractures within each category of mother, father, both parents, either parent and neither parent.

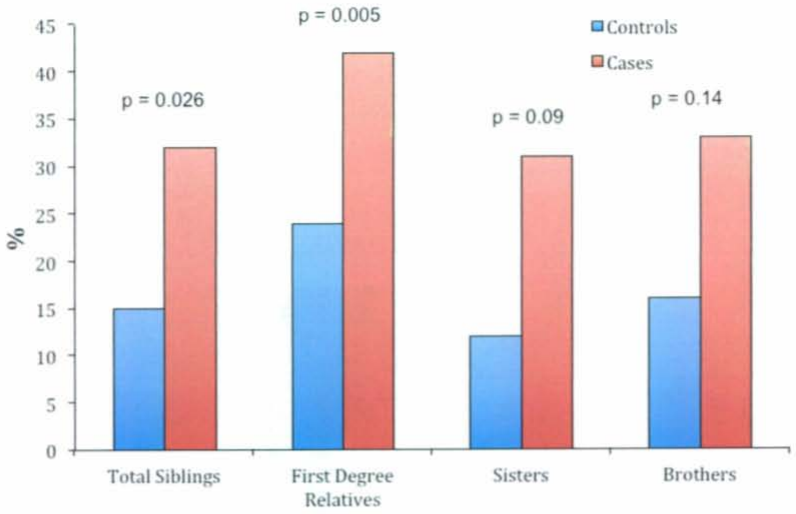

Figure 3-3. Proportion of first-degree family members with fractures for cases vs. controls. First-degree relatives denote a combination of biologic parents and siblings. The p value is testing the significance of the difference between the cases and the control groups for the occurrence of fractures within each category of total siblings, first-degree relatives, sisters and brothers.

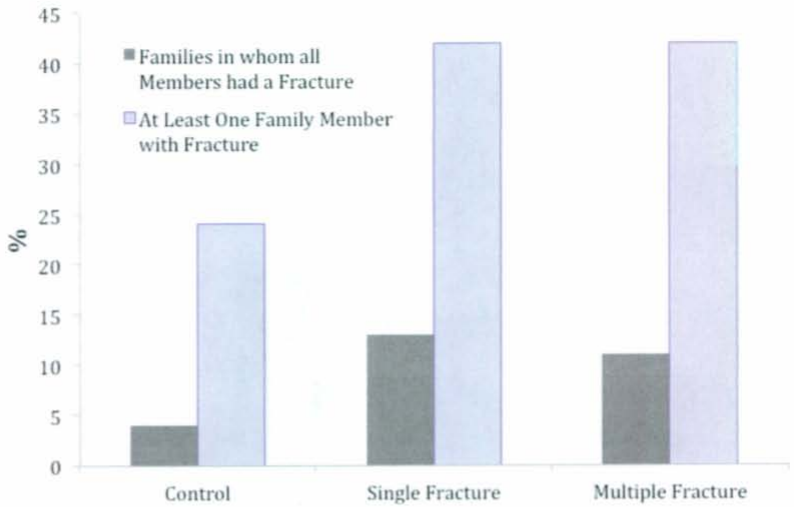

Figure 3-4. Occurrence of fractures in families (Proportions of first-degree family members with fractures).

CHAPTER 4: Discussion

Chapter 4:1 Population characteristics were similar between groups

As derived from data from the national CHIRPP surveillance program, seventeen percent of all injuries seen in the Janeway Emergency Department were fractures. The CHIRPP surveillance program, while an essential source of injury surveillance data, currently is limited by inclusion of only four general hospitals along with the 10 Canadian pediatric hospitals. As children in Canada are more frequently treated for illness and injury in general hospitals, this data will be an underrepresentation of the fracture burden actually experienced. While several large epidemiological studies on pediatric fractures exist (Cheng, & Shen 1993; Cooper et al 2004; Jones et al 2002; Khosla et al 2003; Landin 1997; Lyons et al 1999) North American studies more pertinent than the current Canadian CHIRPP surveillance program have not been found.

Baseline characteristics such as age, ethnicity and parental age were similar between cases and controls and even though boys were more heavily represented amongst cases (62 % vs. 53 %) the difference was not statistically significant. Boys had a slightly higher mean total number of fractures (1.4 vs. 1.2) and more boys were represented in the multiple fracture group (25% vs. 20%) but again these differences were not statistically significant. These findings are similar to that previously reported (Cheng, & Shen 1993; Hagino et al 2000; Hedlund, & Lindgren 1986; Landin 1983; Landin 1997). Theories suggested for boys trending towards higher fracture rates include more risk taking behaviors.

A dissimilar pattern of fracture locations existed between boys and girls. As in previous reports, forearm fractures accounted for nearly half of all fractures although girls were disproportionally represented here (63% of girls; 37 % of boys) which differs from larger studies (Brudvik, & Hove 2003; Jones et al 2002; Landin 1983; Landin 1997; Lyons et al 1999; Lyons et al 2000). The second most common fracture location, the leg, was also found more frequently in girls (23% vs. 10%). The majority of other fracture types were found in boys.

Chapter 4:2 A family history of fractures amongst parents is an important and useful risk factor for childhood fractures

This is the first study that reports odds ratios of fracture risk in children based on parental history of fracture. In this study, the strongest risk for fracture in a child (nearly 4 x) is present when both parents have fractured, (OR 3.7, $p = 0.009$). If either parent has fractured, the risk of fracture for a child is doubled (OR 2.1, $p = 0.042$). A child whose parents are fracture-free has a decreased risk of fracture (OR 0.5,$p=0.042$). Children who have fractured have a 1.4 times greater risk of having a parent who has fractured than children who are fracture free.

To date, only one other study of childhood fractures reports a family history of fractures in parents. Konstantynowicz's survey of Polish adolescents found that fractures in mothers and siblings accounted for 44% of the accountability in adolescents' fractures (Konstantynowicz et al 2005). In adults, Kanis' meta-analysis of prospective data-bases revealed that a parental history of fracture imparted an increased risk of fracture that was

independent of BMD and was higher when combined with sibling history for some fracture types (Kanis et al 2004).

Chapter 4:3 Sibling history may be a risk factor for childhood fracture

The strength of potential contribution of this risk factor is generally difficult to quantify. Sibling numbers vary between families and fracture burden may be underestimated due to some siblings not yet reaching an age that would allow increased risk of fracturing to become apparent. Also, sibling fractures may reflect a common environmental aspect, which influences similarity between siblings. Nevertheless, trends indicate that this factor warrants further exploration in longitudinal or larger studies. Of note, the cases group contains double the burden of fractures from siblings (32% vs. 15%) and double the burden of fractures from first-degree relatives (42% vs. 24%). Risk ratio estimates reveal that cases are twice as likely as controls to have a sibling with a fracture and 1.5 times as likely to have a first degree relative with a fracture. Furthermore, out of 150 study subjects, only 13 families contained family members all of whom had sustained fractures. Ten (77 %) of these were found in the cases group and only 3 (23%) amongst the control group. While numbers are small, interesting trends regarding first-degree relative fracture burden are demonstrated.

Familial aggregation of a multi-factorial trait, such as childhood fractures, is typically evaluated in family studies by examining the proportion of relatives of the proband who also have the trait and comparing it with the proportion of relatives of control subject who do not have the trait. The risk ratio for relatives is a powerful

approach to judging the strength of the effect. For our primary outcome we chose to look at parents rather than siblings, as they were more accessible and had sufficient time to develop a fracture. The relative risk in siblings, which is the traditional measure used to assess familial aggregation, was a secondary outcome. As childhood fractures are common, we do realize that the magnitude of the relative risk will be smaller as compared to a rare disease. This does not necessarily reflect a smaller effect, but rather is a limitation of this method of familial aggregation.

Familial aggregation may be due to environmental or genetic factors. Classic twin studies are often used to disentangle genetic and environmental factors by assessing the concordance rates among monozygotic (MZ) and dizygotic (DZ) twins. For a genetic disease, the concordance rate for MZ twins will be considerably higher than for DZ twins The ideal study design would involve a twin study where the twins were separated at birth. In this way one can assess the impact of identical and non-identical twins who were exposed to differing environments. However collecting such patients is extremely difficult.

Chapter 4:4 Differences in environmental risk factors were not demonstrated in this study

In this study, the only risk factors for fracture that differed between cases and control were family history. Some environmental risk factors for fracture were examined but those did not differ between groups. Specifically with respect to diet, neither calcium, milk nor cola consumption differed between cases and controls. This is similar to Konstantynowiczs' study. A few previous studies have suggested that low milk intake is

associated with fracture. A negative influence of carbonated beverages on bone health has been found in some but not all previous studies. Alcohol, caffeine and cigarette use was denied by our population. Multivitamin was not an exclusion criterion but interestingly was not commonly mentioned under "Are you taking any medications?" Other studies have found a higher physical activity in males than females although we did not find that in this study. Our physical activity questionnaire was not validated and this may have played a role here. Of consideration, the environmental risk factors assessed in this study were largely limited to those pertaining to diet and activity.

Many other risk factors that were not assessed in this study may well be relevant in interpretation of results. As previously discussed and as noted in other studies, comorbidities such as those related to attention, hyperactivity and conduct might differ between the groups and may be found in higher proportions in fracture groups. Furthermore, social circumstances such as socioeconomic level and living situations such as urban vs. rural may result in variable risk of trauma and thus variable opportunities to fracture. Future studies should attempt to better assess a broader range of environmental risk factors as these relevant factors may largely or in part explain observed differences between case and control groups. Of course, it is difficult or impossible to assess all possible risk factors for any given entity and results should always be interpreted with an understanding of this limitation.

Chapter 4:5 Multiple fractures, previous fractures and early age of fracture may be risk factors for fracture

In this current report, 23% of children had multiple fractures with a higher proportion of boys noted, and trends towards increased parental fracture burden were seen in this group as compared to children with a single fracture only. Disease severity (as defined by multiple fractures) was associated with trends to stronger familial aggregation as fractures were present in 84% of parents (58% of mothers) of multiple fracture cases compared to 67% of parents (33% of mothers) of single fracture cases.

Few studies have previously examined multiple fractures as a risk factor for future fractures in children. Goulding et al reported that multiple fractures accounted for up to 60% of all fractures in children. Konstantynowicz et al noted that 12% of adolescents surveyed had multiple fractures (39% of all fractures). The results of this current study show that multiple fractures accounted for 44% of all fractures. Children who sustain multiple fractures tend to bear a sizeable fracture burden even though they represent a small proportion of the fracture population. They may have underlying risk factors that differ from other children.

Several studies in adults have reported the predictive nature of current fracture for future fractures (Cuddihy et al 1999; Eastell 1996). This has also been demonstrated in pediatrics with hazard ratios for further fracture of 1.90 (5% CI 1.50-2.49) after the first fracture and 3.04 (95% CI 2.23 -4.15) after the second fracture (Goulding et al 2005; Goulding et al 2000). Pediatric studies have also observed that fractures tend to occur earlier in life for those who later suffer repeat fractures (Goulding et al 2005; Yeh et al

2006). The early appearance of fractures is more readily understood in the context of a background of genetic susceptibility to fracture although environmental influences may also have a large influence.

Chapter 4:6 Several biases may have influenced the validity of the results

Recall of family history is subject to error although the error should be reasonably distributed between the two groups. It may result, in an underestimate of the association between family history and risk of fracture. However, reporting bias in which subjects with a fracture are more likely to remember a family history of the same condition than those who do not, may also have affected this study, and this could have seriously impacted the results in the direction of the findings – thus overestimated the effect. The impact of this bias could be minimized with a prospective cohort design in which family history is collected before fractures occur. With the current design, review of medical records for the family members may have helped to verify memory of events. This was not done as it was logistically difficult and expensive and may have been limited for relatives incurring medical care in other regions, as charts could not be reasonably accessed. With the advent of electronic medical records, an attempt to minimize this bias could be easier to achieve, should a similar study be repeated.

A time-lag bias may have played a role in this study and this feature should be considered while interpreting the results. The cases (mean 10 years) were somewhat older than the controls (mean 8.8 years), ($p = 0.05$). This could reflect that the cases (and their relatives) had more time to develop fractures and this could contribute as an explanation

as to why the rate of fractures in these families was higher. We had initially hoped to match the children to minimize this bias but unfortunately recruitment did not go as planned and thus the ability to match appropriately was compromised.

Estimates of force were not validated and were constructed by the research team. With respect to estimates of force, little exists in the literature and estimates are difficult to quantify. The simple scale used in this study was based on logical and common clinical estimates but may lack accuracy, as quantification in comparable units cannot be achieved. The physical activity and dietary questionnaire are also subject to recall bias however this information was recorded similarly across groups.

This study did not ascertain whether the family risk of fracture operates independently of BMD. The original design of this study included BMD measurement of each study subject but unfortunately, due to a change in access to the clinical bone densitometer and high clinical demand during this study period, that aspect had to be removed. Physical parameters such as BMI and skin fold thickness would have helped to address the effect of obesity or other physical differences on fractures but similarly due to staffing challenges during the study period, this aspect also had to be removed.

The strong response rate was likely achieved as subjects were captured during their ED visit, filled out the forms while waiting and may have benefited from the presence of a research assistant to collect the forms. However, 15 questionnaires were either entirely illegible (2 cases group) or key information such as the details of family history and environmental risk factors was missing (13 total – 8 control group and 5 cases

group). Although several techniques for dealing with missing data exist (Finch 2010), the extent of the gaps was such that these surveys were considered to be of no use. This resulted in a loss of power and may well have resulted in biasing of parameter estimates. Had this information been available, the results may have been different and several possibilities, including the finding of no association between parental and childhood fractures or a stronger or weaker association, remain.

Ascertainment bias was at a minimum because despite being a tertiary hospital, our center is the only pediatric emergency in the city. Thus most fractures (mild and severe) would be referred to this site. This study is otherwise subject to the limitations of case control studies including an inability to directly measure absolute risk. However, within the limitations of the current design, it appears that family history of fracture has an association with increased risk of fracture in the individual child.

Chapter 4:7 Family history and risk of future fracture

In summary, our primary data suggests there is an association between fractures in parents and in their children, as 48% of parents of cases had sustained fractures as compared to 31% of controls, p=0.007. The familial association was strengthened by the following secondary results:

- Relative risk ratio for siblings among cases is also higher (32%) than in controls (15%), p = 0.026.
- Both parents were more likely to have fractures in the cases (25%) as compared to controls (8%) (OR 3.7, p=0.009)

- Relative risk ratio for total first-degree relative fracture burden was higher in cases (42%) vs. controls (24%), $p = 0.005$.
- Disease severity (as defined by multiple fractures) is also associated with trends to stronger association, as fractures were present in 84% of parents (58% of mothers) of multiple fracture cases compared to 67% of parents (33% of mothers) of single fracture cases.

Chapter 4:8 Clinical applications

If confirmed in future studies, the risk factor of family history (as a risk factor for future fracture) is intuitive and straightforward to ascertain clinically, and thus may be of use in identification of those patients suited for, and motivating compliance with, subsequent intervention. Similarly, given that young age at presentation for fracture confers increased risk of future fractures, young children with first fracture should also undergo focused preventative counseling. Counseling should focus on methods of optimizing peak bone mass acquisition and minimizing bone loss during growth. Some interventional trials have demonstrated that improved nutrition and weight- bearing exercise can strengthen bone. Other recommendations would include safe play and sports, good nutrition and vitamin D status, maintenance of healthy body weight and smoking avoidance. Also, the importance of intervention during prenatal and intrauterine life, to optimize epigenetic, cell differentiation and hormonal outcomes for bone mineralization, should not be overlooked. Therefore promotion of health, lifestyle, wellness and nutrition to women of reproductive age is necessary to provide a good foundation for the bone health of children.

Chapter 4:9 Future research

This study provides important evidence supporting the need to further investigate the basis of common childhood fractures. Ascertainment bias, age and sex adjusted rates of disease, confounding genetic and environmental factors may distort the degree of association and thus replication studies would be prudent. Ideally, a larger case control study with greater statistical power would be needed in order to seek replication of these results. Revised study design with attention to minimizing the biases described in the limitations section would be ideal. Important considerations include: a mechanism to verify occurrence of fractures in family members through medical record review; use of validated environmental assessment tools; age and sex matching of cases and controls. Furthermore, exploration of a broader range of environmental influences on fracture rates with attention to the role of behavioral and risk-taking modifiers is essential. Additionally, certain fracture types may have stronger familial associations than others and the risk may not be equal across fracture sites. Additional details on family history, including details of fracture sites in first-degree relatives, would allow exploration of strength of associations of variable physical sites.

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CASE/CONTROL REPORT FORM

Principal Investigator: Dr Sarah Curtis

Confirmation

I hereby confirm that data contained in this CRF is correct and complete to the best of my knowledge.

I also confirm that the Subject has given his/her signed Informed Consent to participate in this study.

Date of signature _ _ _ _ _ _ _ _

_____

Signature of Principal Investigator

Appendix A
Curtis: Childhood Fractures Appear to be Heritable: Case/Control Report Form

Demographic Data

Postal Code of Origin __ __ __ __ __ __

Community of Origin _____

Religion (parents)

___ Father ___Mother

1) Catholic 2) Anglican 3) United 4) Salvation Army 5) Others

Date of birth __ __ __ __ / __ __ / __ __ Sex Male __ Female__

Ethnic Group

Please fill ethnic group for each person. Please record further details if answered Caucasian or other.

		Further Details
1. Caucasian (Irish/English/Scottish/French)	Yourself ___	_____
2.Native American Indian	Father ___	_____
3.Indian (east)	Mother ___	_____
4. Black	PGF ___	_____
5. Oriental	PGM ___	_____
6. Unknown	MGF ___	_____
7. Other	MGM ___	_____

PGF/MGF = paternal/maternal grandfather
PGM/MGF= paternal/maternal grandmother

What is your current occupational status? _____
Do you have any of the following conditions? (Please circle)

Hyperthyroidism
Hypothyroidism
Hyperparathyroidism
Hypogonadism
Diabetes
Growth hormone deficiency
Osteoporosis
Cystic Fibrosis
Asthma
Liver disease, celiac disease, Inflammatory Bowel Disease
Spina Bifida
Epilepsy
CP
Neuromuscular disease
Cancer

Yes____ No_____ If yes please specify_____

Do you have any other medical illness? Yes__ No__

If yes please specify_____
_____

Are you taking any medications? Yes___ No___

If yes please specify_____
_____

What medications have you taken in the past?

_____
_____
_____
_____

What was your gestational age at birth? ____Wks

What was your birth weight? ____Lbs ____ Kgs

Were you admitted to the NICU as a neonate?
If yes - why? _____

Have you started your periods? _____

What age were you when you had your first period? _____

Have you gone three or more months without a period? _____ **More than one year?**___

Have you gained or lost weight? If yes how much over what period? _____

Which operations have you had? How old were you?
Operation_____ **Age**_____
Operation_____ **Age**_____
Operation _____ **Age**_____

Have you been confined to a bed, wheelchair or cast for more than one month at a time?
_____ **If so, how many times?** _____ **For how long?** _____

How many fractures have you had? _____
What bones did you fracture? _____

Exercise **(please list all regular physical activities)(include brisk walking….)**

Activity _____ Hours / week_____
Activity _____ Hours / week_____
Activity _____ Hours / week_____
Activity _____ Hours / week_____
Activity _____ Hours / week_____
Activity _____ Hours / week_____
Activity _____ Hours / week_____
Activity _____ Hours / week_____

How many hours a day do you spend sitting in general? (Include work, school, TV, meals)_____
How many hours a day do you sleep? _____

Do you smoke? Yes___ No___ # cigarettes/day_____
Are you exposed to the tobacco smoke of others? _____ hours/day _____years

Do you consume alcohol? Yes___ No___
If yes, how much? _____(drinks/week)

Sunlight

How often do you expose your body to direct sunlight? (circle)

Never body parts_____, _____, _____
Seldom body parts_____, _____, _____
Regularly body parts_____, _____, _____
Often body parts_____, _____, _____

Do you use a sunscreen product when in direct sunlight? (circle)

Never body parts_____ SPF_____
Seldom body parts_____ SPF_____
Regularly body parts_____ SPF_____
Often body parts_____ SPF_____

Diet
How often do you eat the following?

Food	Never	Servings Year	Month	Week	Day
Coffee Caffeinated (1 cup)					
Tea Caffeinated (1 cup)					
Colas Caffeinated (1 can)					
Alcohol (1 beer/ 1 glass wine)					
Canned salmon/sardines with bones					
Broccoli					
Dark leafy greens, collards					
Dried peas or beans					
Whole wheat bread, bagels, buns					
White bread, bagels, buns					
Tofu					
Multivitamin, vit. D or cod liver oil					
"TUMS" or calcium supplements					
Milk to drink incl chocolate milk					
Milk on cereal					
Milk/cream in tea coffee					
Milk deserts (tapioca, rice pudding)					
Hard cheese					
Yogurt					
Ice-cream, frozen yogurt					
Soups made with milk					

Circumstances Surrounding this Fracture

In a few sentences please describe how you obtained this fracture below.
What activities were you engaged in at the time? (walking,running,jump,fall,bike,skateboard,car)
Estimate the distance you fell. (From standing, bike, board, wall… moving or stationary?)
Did you twist the limb involved?

Family History

How many sisters do you have? ___

How many of your sisters have had a fracture(s) in the past? ____(# of sisters)

How many fractures has each sister had?

1. ____(# fractures) _____(age of sister now) _____ (medical condition)
2. ____(# fractures) _____(age of sister now)_____ (medical condition)
3. ____(# fractures) _____(age of sister now)_____ (medical condition)
4. ____(# fractures) _____(age of sister now)_____ (medical condition)
5. ____(# fractures) _____(age of sister now)_____ (medical condition)
6. ____(# fractures) _____(age of sister now)_____ (medical condition)

How many brothers do you have? ___

How many of your brothers have had a fracture(s) in the past? ____(# of brothers)

How many fractures has each brother had?

1. ____(# fractures) ___(age of brother now) _____ (medical condition)
2. ____(# fractures) ___(age of brother now) _____ (medical condition)
3. ____(# fractures) ___(age of brother now) _____ (medical condition)
4. ____(# fractures) ___(age of brother now) _____ (medical condition)
5. ____(# fractures) ___(age of brother now) _____ (medical condition)
6. ____(# fractures) ___(age of brother now) _____ (medical condition)

What age is your mother? ____yrs _____ # of fractures _____(medical condition)
What age is your father? ____yrs _____ # of fractures _____(medical condition)

Do any of your family members have any medical conditions? (List above)

That ends the questionnaire.
Thank you for participating.

Parental Report Form

Principal Investigator: Dr Sarah Curtis

Confirmation

I hereby confirm that data contained in this PRF is correct and complete to the best of my knowledge.

I also confirm that the Subject has given his/her signed Informed Consent to participate in this study.

Date of signature _ _ _ _ _ _ _ _

_____
Signature of Principal Investigator

Demographic Data

Postal Code of Origin __ __ __ __ __ __

Community of Origin _____

Religion (parents) ___ Father ___Mother

1) Catholic 2) Anglican 3) United 4) Salvation Army 5) Others

Date of birth __ __ __ __ / __ __ / __ __ Sex Male __ Female__

Ethnic Group

Please fill ethnic group for each person. Please record further details if answered Caucasian or other.

Details		Further
1. Caucasian (Irish/English/Scottish/French)	Yourself ___	_____
2.Native American Indian	Father ___	_____
3.Indian (east)	Mother ___	_____
4. Black	PGF ___	_____
5. Oriental	PGM ___	_____
6. Unknown	MGF ___	_____
7. Other	MGM ___	_____

Do you have any of the following conditions?
Hyperthyroidism
Hypothyroidism
Hyperparathyroidism
Diabetes
Growth hormone deficiency
Osteoporosis
Cystic Fibrosis
Asthma
Liver disease
Celiac disease,
Inflammatory Bowel Disease
Spina Bifida
Epilepsy
CP
Neuromuscular disease

Yes____ No_____ If yes please specify_____

Do you have any other medical illness? Yes__ No__

If yes please specify_____
_____

Are you taking any medications? Yes___ No___

If yes please
specify_____
_____

What medications have you taken in the past? _____

Do you smoke? Yes___ No___

Do you consume alcohol? Yes___ No___
If yes, how much? _____(drinks/week)

How many fractures have you had? _____fractures.

Marital Status

Single___ Married___ Widow___
Divorced Separated__ Common Law__

Education

<Grade 8___ Grade 8___ High School___ College___ University___

Employment Status

Employed___ Homemaker___ Student___Disabled___ Retired___

Household Income Level

<12,000___ 12,000- 30,000___ 30,000-60,000___ >60,000___

Family History

How many sisters do you have? ___ How old are they? __/__/__/__/__/__/yrs

How many of your sisters have had a fracture(s) in the past? ____(# of sisters)
How many fractures has each sister had? ____(#of fractures) ___(age of sister now)
____(#of fractures) ___(age of sister now)
____(#of fractures) ___(age of sister now)
____(#of fractures) ___(age of sister now)
____(#of fractures) ___(age of sister now)
____(#of fractures) ___(age of sister now)

How many brothers do you have? ___ How old are they? __/__/__/__/__/__/yrs

How many of your brothers have had a fracture(s) in the past? ____(# of brothers)
How many fractures has each brother had? ____(#of fractures) ___(age of brother now)
____(#of fractures) ___(age of brother now)
____(#of fractures) ___(age of brother now)
____(#of fractures) ___(age of brother now)
____(#of fractures) ___(age of brother now)
____(#of fractures) ___(age of brother now)

What age is your mother? ____yrs # of fractures ____
What age is your father? ____yrs # of fractures ____

That ends the questionnaire.
Thank-you for participating.

Appendix C
Curtis et al.

FORCE OF FRACTURE SCALE

This is an estimate of trauma severity based on a retrospective classification by the primary investigators of the description of events surrounding the fracture.

1. MILD:

    - Generally forces incurred by the injured individual
    - Low velocity
    - Falls less than 0.5-1 meters
    - Falling from standing
    - Tripping when walking /running

2. MODERATE:

    - Generally sporting related injuries
    - Falls 1 - 3 meters
    - Medium velocity
    - Ball sports
    - Skating
    - Gymnastics
    - Rollerblading
    - Biking
    - Skateboarding

3. SEVERE:

    - High velocity
    - Motor vehicle accident
    - Car–pedestrian
    - Falls greater than 3 meters
    - Windows /roofs
    - Falls from horses

Appendix D: Curtis: Childhood Fractures are Heritable

FACULTY OF MEDICINE - MEMORIAL UNIVERSITY OF NEWFOUNDLAND

AND

HEALTH CARE CORPORATION OF ST. JOHN's

Consent To Participate In Bio-medical Research

TITLE: **Childhood Fractures: Assessments of Epidemiology and Genetic Determinants**

INVESTIGATOR(S): Dr. Sarah Curtis, Dr. Proton Rahman, Dr. Pat Parfrey, Dr. Tracey Bridger.

You (or your child or ward) have been asked to participate in a research study. Participation in this study is entirely voluntary. You may decide not to participate or may withdraw from the study at any time without affecting your normal treatment. Information obtained from you or about you during this study, which could identify you, will be kept confidential by the investigator(s). The investigator will be available during the study at all times should you have any problems or questions about the study.

1. Purpose of study:

Fractures are commonplace and are a significant cause of pain and disability in all age groups. Little is known about childhood fractures and fracture risks within families. Your participation in this study may help us to better understand whether or not having family members who fracture puts one at greater risk of having a fracture in the future. We also wish to examine how diet, exercise, sun-light exposure and other environmental factors influence ones risk of having a fracture.

2. Description of procedures:

You have been requested today to participate in this study on the basis that either your child has sustained a fracture (cases) or that your child is similar in characteristics (age, sex) to a child who has had a fracture(control).You and your child will be asked to fill out a case report form. This consists of a general medical history and physical exam to be done by the physician. It also consists of questions relating to fracture histories of family members and environmental aspects such as diet and exercise. Children may have assistance from their parents to complete this form. The parents of both cases and controls will also be administered a parent report form. This consists of a general medical history, questions relating to fracture histories of family members and environmental aspects such as diet and exercise.

3. Duration of participant's involvement:
   The study will begin in May 2001 and will run for one year. Your participation will involve a thirty-minute case report form only as described above.

4. Possible risks, discomforts, or inconveniences:
   The main inconveniences of participating in this study are that of the time required to fill out the form. There are no known harms.
5. Benefits which the participant may receive:
   There is no immediate benefit to you to participate in this study.

6. Liability statement.
   Your signature indicates your consent and that you have understood the information regarding the research study. In no way does this waive your legal rights nor release the

Appendix D: Curtis: Childhood Fractures are Heritable
FACULTY OF MEDICINE - MEMORIAL UNIVERSITY OF NEWFOUNDLAND
AND
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investigators or involved agencies from their legal and professional responsibilities.

Title: **Childhood Fractures: Assessments of Epidemiology and Genetic Determinants**

Investigators :Dr. Sarah Curtis, Dr. Proton Rahman, Dr. Pat Parfrey, Dr. Tracey Bridger.

To be signed by participant

I,_____, the undersigned, agree to my participation or to the

participation of_____ (my child, ward, relative) in the research study described above.

Any questions have been answered and I understand what is involved in the study. I realize that participation is voluntary and that there is no guarantee that I will benefit from my involvement.

I acknowledge that a copy of this form has been given to me.

(Signature of Participant)_____(Date)_____

(Signature of Witness)_____ (Date)_____

To be signed by investigator

To the best of my ability I have fully explained the nature of this research study. I have invited que and provided answers. I believe that the participant fully understands the implications and voluntar of the study.

(Signature of Investigator)_____(Date)_____

Phone Number

Assent of minor participant (if appropriate)

(Signature of Minor Participant) _____ (Age)_____

Relationship to Participant Named Above _____